IEc

Literature Review of Air Pollution-Related Health Endpoints and Concentration-Response Functions for Ozone, Nitrogen Dioxide, and Sulfur Dioxide:

Results and Recommendations

Draft Report | October 2, 2015

INDUSTRIAL ECONOMICS, INCORPORATED

IEc

TABLE OF CONTENTS

RECOMMENDATIONS SUMMARY *31*

REFERENCES *33*

IEc

INTRODUCTION

Every four years, the South Coast Air Quality Management Board (SCAQMD) updates the regional Air Quality Management Plan (AQMP) for Los Angeles, Orange, Riverside, and San Bernardino Counties in southern California. As part of the development of this Plan, SCAQMD considers the socioeconomic impacts of the AQMP. These estimated benefits and costs are detailed in a Socioeconomic Report that accompanies the AQMP.

A key analysis in the Socioeconomic Report is an assessment of the health benefits of the AQMP on residents of these four counties. This assessment of health impacts relies on data describing the baseline incidence of mortality and morbidity endpoints, the estimated change in air pollution concentrations, and the relationship between exposure and health outcomes. SCAQMD draws this latter input from population-based epidemiological studies. These studies provide information on which health endpoints are associated with exposure to air pollutants, and the mathematical relationship between exposure and the outcome. This report presents our review of recent studies of the health impacts associated with exposure to ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) and provides recommendations to inform SCAQMD's decisions regarding which health endpoints to include in its benefits analysis of the 2016 AQMP and which mathematical functions should be used to evaluate each endpoint.

The remainder of this document describes the methods we employed for our literature search and evaluation of the studies we identified and presents the results of our search. Finally, we summarize our recommendations to the SCAQMD for the health endpoints to include in its 2016 Socioeconomic Assessment as well as the study or studies that should serve as the basis for quantifying each of those endpoints.

METHODS

Our approach consisted of three steps. First, we identified the endpoints and studies used in EPA's National Ambient Air Quality Standards (NAAQS) Regulatory Impact Assessments (RIA). Second, we reviewed the current evaluation of O_3, NO_2, and SO_2 effects by the U.S. Environmental Protection Agency (EPA) in its most recent Integrated Science Assessment (ISA) document (U.S. EPA, 2009). Finally, we conducted a review of the health literature.

EPA NATIONAL AMBIENT AIR QUALITY STANDARDS REGULATORY IMPACT ANALYSES

Because the 2012 Socioeconomic Report for the South Coast AQMP did not include health assessments for O_3, NO_2, and SO_2, we investigated U.S. EPA's RIAs to better understand which studies EPA has used since 2012 (ozone) or 2010 (NO_2, SO_2).

EPA INTEGRATED SCIENCE ASSESSMENT

In addition to our literature review, we also reviewed the most recent Integrated Science Assessment for PM published by the EPA in 2009. The comprehensive assessment of the health literature presented in the ISA provides EPA's current assessment of the strength of the evidence linking PM exposures with an array of health endpoint categories and thus serves as a suitable baseline against which we can compare the findings of recent research.

SUPPLEMENTAL LITERATURE REVIEW

In order to ensure SCAQMD uses the most current science when evaluating the health impacts of air pollution control, we conducted a literature review on mortality and morbidity impacts of O_3, NO_2, and SO_2. We searched PubMed and Google Scholar for peer-reviewed articles on these pollutants from 2003 onward (SO_2), 2007 onward (O_3), and 2012 onward (NO_2), using search terms "[pollutant] AND mortality" and "[pollutant] AND morbidity," where [pollutant] was O_3, NO_2, or SO_2. We additionally performed a separate search on "Ozone AND Asthma AND California" to ensure we had the latest studies on this key endpoint specific to the region of study. We also included several studies that did not appear in our search but were recommended by our scientific advisor, Dr. George Thurston. We prioritized studies to evaluate for inclusion in the Socioeconomic Assessment by evaluating them using the criteria described in our Evaluation Criteria Memo to SCAQMD dated August 20, 2015; these criteria are

IEc

summarized in Exhibit 1. Our criteria serve as guidance for evaluating studies and weighing their strengths and limitations. No one study is likely to meet all criteria listed.

EXHIBIT 1.   CRITERIA FOR EVALUATING EPIDEMIOLOGICAL STUDIES

CRITERIA
GENERAL:

1. Study is peer-reviewed.
 2. Study is written in English.
 3. Study measures exposure to at least one of the following pollutants: O_3, $PM_{2.5}$, PM_{10}, NO_x, SO_2,
 4. Preference given to studies or groups of studies that significantly advance our understanding of the relationship between air pollution exposures and mortality and morbidity endpoints, including those endpoints previously quantified by the SCAQMD in its Air Quality Management Plans as well as new endpoints.
 5. Study was published within the following timeframes:
     a. $PM_{2.5}$/PM_{10}: 2012 – present
     b. NO_2: 2012 – present
     c. O_3: 2007 – present
     d. SO_2: 2003 - present

GEOGRAPHY AND STUDY POPULATION:

6. Study measures exposures at or near ambient levels found in the South Coast Air Basin. Order of preference of study location:
     a. South Coast Air Basin (Los Angeles, Orange, Riverside, and San Bernardino Counties)
     b. Within State of California
     c. Within Western United States
     d. Within United States or Canada
 7. Study uses study population with similar characteristics as found in Los Angeles, Orange, Riverside, and San Bernardino counties.

STUDY DESIGN:
8. Study is population-based, preferably using cohort or case-control epidemiological study designs. Controlled human exposure studies may be evaluated for supporting evidence, or in the absence of relevant epidemiology. Animal and in-vitro studies excluded.   9. Study controls for factors that may obscure the true concentration-response relationship, including selection bias, misclassification, recall bias, confounding (including by other pollutants), effect modification, mortality displacement, loss to follow-up, etc.   10. Study appropriately assesses any potential lag between exposure and outcomes.   11. Study appropriately assesses any potential exposure thresholds for health outcomes.   12. Study clearly presents information about uncertainty in results to facilitate evaluation and comparison with other studies.   13. Prefer studies that assess changes in the risk of incidence of disease, rather than exacerbation of existing cases or changes in symptoms.

IEc

RESULTS

In this section, we review studies found during this literature review and compare these findings to studies employed by EPA in its most recent NAAQS RIAs for ozone (2014), nitrogen dioxide (2010), and sulfur dioxide (2010),. All three RIAs quantified the morbidity endpoints of asthma emergency department visits, asthma exacerbation, acute respiratory symptoms, and respiratory hospital admissions (all respiratory for O_3 and SO_2, asthma and chronic lung disease for NO_2). Only the O_3 RIA quantified impacts from school loss days and mortality. In the NO_2 RIA, where EPA used more than one study, EPA chose a random/fixed effects pooling, except for asthma studies, as described below. The pooling methods for other RIAs are detailed in each section. We do not detail studies that only include lung function metrics (e.g., Gauderman et al. 2015) because EPA does not quantify or monetize this endpoint. Below we detail studies from our literature review that focus on populations in California, the western U.S., or nationwide. We discuss whether the studies from U.S. EPA's RIAs are appropriate to apply to SCAQ's assessment of air pollution-related health impacts in southern California or whether we recommend updating the concentration-response function based on our review of more recent literature.

EXHIBIT 2.   OVERVIEW OF STUDIES IN EPA NAAQS RIAS FOR O₂, NO₂, AND SO₂

ENDPOINT GROUP	ENDPOINT	STUDY	AGE RANGE EPA APPLIED EFFECTS ESTIMATES
2014 Ozone NAAQS RIA			
Premature mortality	Short-term mortality	Smith et al. (2009); Zanobetti and Schwartz (2008)	All ages
	Long-term respiratory mortality incidence	Jerrett et al. (2009)	>29
Hospital admissions	Respiratory (all)	Katsouyanni et al. (2009)	>65
	Asthma-related	Glad et al. (2012); Ito et al. (2007); Mar and Koenig (2009); Peel et al. (2005); Sarnat et al. (2013); Wilson et al. (2005)	0-99
Other	Asthma Exacerbation	Mortimer et al. (2002); O'Connor et al. (2008); Schildcrout et al. (2006)	6-18

ENDPOINT GROUP	ENDPOINT	STUDY	AGE RANGE EPA APPLIED EFFECTS ESTIMATES
	School loss days	Chen et al. (2000); Gilliland et al. (2001)	5-17
	Acute respiratory symptoms/minor restricted activity days	Ostro and Rothschild (1989)	18-65
2010 Nitrogen Dioxide NAAQS RIA			
Hospital admissions	Asthma	Linn et al. (2000)	All ages
	Chronic lung disease	Moolgavkar (2003)	>65
Emergency department visits	Asthma	Ito et al. (2007); NYDOH (2006); Peel et al. (2005)	All ages
Other	Asthma exacerbation	O'Connor et al. (2008); Ostro et al. (2001); Schildcrout et al. (2006)	4-12
		Delfino et al. (2002)	13-18
	Acute respiratory symptoms	Schwartz et al. (1994)	7-14
2010 Sulfur Dioxide NAAQS RIA			
Hospital admissions	Respiratory (all)	Schwartz et al. (1996)	65-99
Emergency department visits	Asthma	Ito et al. (2007); Michaud (2004); NYDOH (2006); Peel et al. (2005); Wilson (2005)	All ages
Other	Asthma exacerbation	Mortimer et al. (2002); O'Connor et al. (2008); Schildcrout et al. (2006)	4-12
	Acute respiratory symptoms	Schwartz et al. (1994)	7-14

MORTALITY

CAUSALITY - OZONE

In its 2013 ISA document, EPA concludes that there is likely to be a causal relationship between short-term ozone exposures and mortality, and that the evidence linking long-term ozone exposure with mortality is suggestive of a causal relationship. EPA based its findings for short-term mortality effects on the addition of a number of multicity studies and a multi-continent study to the base of literature that previously suggested a short-term effect. The newer studies found consistent, positive associations of short-term ozone exposure with both total and cause-specific mortality, typically showing stronger effects in the warm season. Associations between long-term ozone exposure and mortality are less conclusive at this time; results for cardiovascular mortality are mixed and evidence

of a link to total mortality is limited. The strongest evidence for long-term exposure to ozone is for a link to respiratory mortality. These mixed findings and limited database led EPA to classify the evidence linking long-term exposure to mortality ozone as only suggestive of a causal relationship. These findings largely echo the findings of a 2008 National Academy of Sciences (NAS) panel that reviewed the ozone/mortality relationship. The NAS panel found the array of multi-city time series studies and meta-analyses conducted in the early 2000s provided "robust statistical evidence of an association", leading them to conclude that short-term ozone exposure "is likely to contribute to premature deaths" (NAS, 2008). They also indicated that the evidence did not support modeling of a threshold for these impacts.

NAS notes potential concern over confounding of ozone-mortality relationship with PM, but also notes that the PM/ozone correlations show considerable variation location to location. Thus, the assessment of any degree of confounding is far from straightforward and may vary spatially. A reanalysis of NMMAPS data for 98 urban communities by Bell et al. (2007) found no evidence that PM_{10} or $PM_{2.5}$ confounds the short-term ozone/mortality relationship, while an analysis of 18 U.S. communities by Franklin and Schwartz in 2008 showed some confounding of this relationship by sulfate particles, which are largely comprised of secondary pollution formed in the atmosphere, like ozone. Given the lower concentrations of sulfate particles in the South Coast study area, these two studies suggest that assessing an independent mortality effect of ozone, at least on short-term deaths, may be reasonable for the 2016 Socioeconomic Assessment.

The studies we found in our supplemental literature review were consistent with the above EPA and NAS findings regarding causality and threshold.

CAUSALITY - NO2 AND SO2

EPA's 2008 ISA document for NO_2 found that the evidence linking short-term NO_2 to total nonaccidental and cardiopulmonary mortality was "suggestive but not sufficient" to infer a causal relationship. While EPA found that studies generally reported positive associations, EPA found little evidence to evaluate the coherence and plausibility of these findings, especially given difficulties teasing out the effects of NO_2, which contributes to the nitrate portion of PM, from the effects of the overall PM mass. They found the evidence supporting a mortality association with long-term exposure to be "inadequate to infer the presence or absence of a causal relationship" (EPA, 2008) because of inconsistent results in U.S. and European cohort studies and issues of co-pollutant confounding between NO_2 and PM.

Findings for SO_2 are similar to those for NO_2; EPA found consistently positive associations with SO_2 on all-cause and cardiopulmonary mortality, but these results were not robust in multipollutant models. Thus, they classified the evidence as only suggestive of a causal relationship between short-term SO_2 exposures and mortality. They found evidence for associations between long-term SO_2 exposure and mortality to be less compelling, due to a lack of consistency across studies and difficulty addressing

confounding by copollutants, and therefore rated the evidence as "inadequate to infer a causal relationship".

Our supplemental literature review did not find sufficient evidence to make a different determination as to whether there is a causal relationship involving independent mortality impacts of either NO_2 or SO_2.

STUDIES FROM U.S. EPA RIAS

In its most recent RIA for the Ozone NAAQS, EPA pooled the results of two studies for short-term ozone mortality. The first, Smith et al., 2009 conducted an extensive meta-analysis of time series studies of the short-term ozone-mortality effect from around the world. While we agree this is a high quality study, a large proportion of the inputs from the meta-analysis come from international studies, which may or may not be as relevant for application to a specific U.S. city. We prefer to focus our review for SCAQMD on the pool of Los Angeles-specific estimates we found from similarly high quality studies, including the second RIA study: Zanobetti and Schwartz, 2008.

STUDIES FROM LITERATURE REVIEW: MORTALITY

Our supplemental literature review found two studies addressing ozone exposure and infant mortality and 26 studies addressing ozone exposure and mortality in adults that reported results for the city of Los Angeles, all or part of California, or the U.S. as a whole including western U.S. cities. All studies identified in our search are listed in Appendix A.

Infant mortality

Of the two studies addressing infant mortality, one (Ritz et al, 2006) was conducted in the South Coast Air Basin, but the authors did not find associations between ozone exposure and all cause death or sudden infant death syndrome (SIDS) in infants. The other study by Woodruff et al (2008) did not find an association with infant respiratory deaths and ozone, but did find an association between ozone exposure and SIDS. These studies do not provide sufficient evidence to recommend evaluating infant mortality from ozone exposures.

Adult mortality - ozone

Of the 28 studies addressing ozone exposure and mortality, three addressed only long-term exposures, one (Smith et al., 2009) addressed both, and the remainder addressed short-term exposure.

Of the 24 short-term studies, we eliminated two that focused on addressing specific issues of susceptible populations (Medina-Ramon and Schwartz 2008 and Zanobetti and Schwartz 2011) and one that focused on deaths only from chronic lower respiratory disease (Hao et al., 2015). Within the remaining set, we focused on studies in Exhibit 3 that reported an estimate of effect in Los Angeles or Southern California, either as an part of a multi-city analysis or meta-analysis, or as an input to a meta-analysis.

- **Bell and Dominici, 2008** reanalyzed data from 1987 to 2000 for 98 U.S. urban communities from the National Morbidity, Mortality, and Air Pollution (NMMAPS) dataset to identify whether community characteristics modified the effect of ozone on mortality found in past NMMAPS analyses. They found higher estimates associated with factors such as higher unemployment, larger fraction of African American population, public transportation use, and lower prevalence of air conditioning use. This study also presents region-specific mortality effect estimates from NMMAPS results, including one for Southern California for a 0.21 percent (-0.46 – 0.88) increase in mortality for a 10 ppb increase in the previous week's daily O_3.

- **Bell et al 2004 and 2005**. The first of these studies present the results of a multi-city analysis of the NMMAPS data for short-term ozone mortality impacts across 95 U.S. urban communities, using distributed lag models to estimates community specific rates adjusted for key time-varying confounding factors such as PM, weather, season, and long-term trends. The 2004 study also applies hierarchical Bayesian methods to integrate community-specific findings into an overall national average rate, controlling for spatial heterogeneity. The second study conducts a meta-analysis of time-series studies of ozone and mortality and compares the results to the 2004 NMMAPS findings. The 2005 study found that meta-analysis results were consistently larger than the NMMAPS results. Los Angeles was among the eight cities for which both results were generated and while the meta-analysis central effect estimate was higher, the difference in the central estimates was considerably smaller than for other cities, as were the reported confidence intervals for both results.

- **Huang et al, 2005.** This is another multi-city time series study analyzing NMMAPS data. This study uses Bayesian hierarchical distributed lag models to estimate the effect of daily summer O_3 concentrations specifically on cardiovascular and respiratory mortality in 19 large U.S. cities, including Los Angeles. Results were sensitive to adjustment for PM_{10} but not influenced by other potential confounders such as long-term trends and other gaseous pollutants. The study reports significant positive associations in LA for models of lags 0, 1, and 2 days (values not reported in study) as well as a positive, but not statistically significant association for the distributed lag result, which is presented in Exhibit 3.

- **Ito et al, 2005** includes a meta-analysis of short-term ozone mortality studies across a wide range of cities from 1990-2003 and conducts additional time-series analysis for 7 U.S. cities. The latter analysis does not include Los Angeles but instead includes primarily East coast or Midwest cities. We nonetheless include this study in Exhibit 3 because it provides estimates from past studies of ozone mortality in LA as inputs to its meta-analysis.

- **Levy et al. 2005** is another meta-analysis of 48 estimates from 28 studies of short-term mortality impacts of ozone that uses Bayesian metaregression methods

to adjust for variation in study design (e.g., statistical methods, inclusion of specific confounding factors). The authors found an overall increase of 0.21% (0.16 – 0.26) in mortality associated with a 10 ppb change in one-hour maximum ozone concentrations, and that air pollution use and lag time explained the greatest proportion of inter-study variability. The study includes estimates of mortality impacts from past studies of ozone mortality in LA as inputs to its meta-analysis.

- **Zanobetti and Schwartz, 2008** is a study that analyzes whether there is mortality displacement (i.e., advancing deaths by a few days) due to ozone exposure that is responsible for the ozone mortality signal. This analysis of results across 48 US cities between 1989 and 2000 found increasing mortality impacts with larger ozone exposure windows, suggesting that use of a single day's ozone concentration is more likely to underestimate the mortality impact of ozone. This paper does include a figure with LA-specific estimates of the mortality effect, though specific numbers are not provided in the text.

All the studies in Exhibit 3 are high-quality studies that are well-documented. In several cases, the LA-specific results are not statistically significant, though the central effect estimates are consistently positive and of similar magnitude. The lack of statistical significance may reflect the impact of extracting city-specific results, with smaller sample size, from larger multi-city studies originally designed to report integrated U.S. estimates. We note, for example, that studies focused on LA that are used as inputs to meta-analyses (Kinney et al., 1995 and Moolgavkar, 2003) have findings that are both positive and statistically significant.

RECOMMENDATIONS: ADULT MORTALITY - OZONE

Of the studies in Exhibit 3, we recommend an equal weight pooling of mortality estimates based on the meta-analysis and NMMAPS results in Bell et al., 2005 for the 2016 Socioeconomic Analysis, provided we can obtain the data for Figure 2 in that paper from the authors. The Bell et al. study has the advantage that the meta-analytic results already incorporate results from LA studies by Kinney et al. 1995, Moolgavkar 2003, and others, and both the meta-analysis and NMMAPS estimates have relatively tight confidence intervals compared with the other studies in the Exhibit. We propose to develop a C-R function applicable to a change in the 8-hour max ozone metric (vs. 24-hour average or 1-hour max), using the conversion ratios applied in the recent ozone NAAQS RIA (U.S. EPA, 2014).

We do not recommend quantifying mortality associated with long-term exposures to ozone at this time. Despite EPA's inclusion of a long-term study in the RIA for the most recent ozone NAAQS (2014) we continued to see mixed results in the recent studies we reviewed and are concerned about the potential for a double-counting of long-term mortality results with PM effects. Of the studies we found, Smith et al. (2009) found no association between ozone and mortality in their analysis of ACS cohort data, and Krewski et al., 2009 had similar results, with the exception of a few associations with

deaths from ischemic heart disease (IHD). Jerrett et al., 2013 found associations of ozone with IHD deaths in California, but not with all-cause, respiratory, or cardiovascular categories. These results became insignificant when combined in a model with $PM_{2.5}$; however, they were significant in a model with both $PM_{2.5}$ and NO_2. In sum, while the results for IHD are potential suggestive of an association, it is not clear whether the effect being measured is attributable to ozone or PM, particularly in California. At this time, we find the evidence is not strong enough for us to recommend quantifying this endpoint for ozone at this time in the South Coast Air Basin.

RECOMMENDATIONS: ADULT MORTALITY NO_2 AND SO_2

Appendix A presents the studies we found addressing mortality impacts of NO_2 and SO_2. In short, we do not see compelling evidence in the studies we found to argue for estimating independent mortality impacts of these gaseous pollutants. Given the previous causality determinations in EPA's ISAs for these pollutants, there would need to be substantial advances in the overall numbers of studies, in the consistency of results, and in the studies that focus on addressing the co-pollutant issues raised by EPA to be able to begin to distinguish separate mortality impacts for NO2 and SO2.

.

EXHIBIT 3. STUDIES THAT REPORT SHORT-TERM OZONE MORTALITY IMPACTS FOR SOUTHERN CALIFORNIA OR LOS ANGELES

STUDY	LA ESTIMATE (% CHANGE IN MORTALITY)	OZONE INCREMENT/METRIC	NOTES
Bell and Dominici, 2008	0.21 (-0.46 - 0.88) for Southern CA	10 ppb daily O_3 previous week	
Bell et al., 2004	~0.2	10 ppb daily O_3 previous week	Estimated from Fig. 2; confidence interval includes zero
Bell et al., 2005	~0.3, ~0.5	lag 0 (NMMAPS); 10 ppb daily O_3 lag 0-2 (meta-anal)	Estimated from Fig 2; lower value from NMMAPS, higher value from meta-analysis; both significant; need data to get specific values and CIs
Huang et al., 2005	0.79 (-0.69, 2.28)	10 ppb daily O_3	CVD and RESP deaths only
Ito et al., 2005	~0.4 , ~0.8	per 20 ppb 24-hr avg. O_3	Estimated from Fig 5; estimates from Kinney et al., 1991, 1995
Levy et al., 2005	0.07 (0-0.17) , 0.1 (0.02 - 0.19)	per 10 µg/m3 increase in 1-h max ozone	From Kinney et al 1995 and Moolgavkar, 2003, respectively
Zanobetti and Schwartz, 2008	between 0 and 0.3	Per 10 ppb increase in 8-hr ozone	Estimated from Fig 1; appears positive but not significant

IEc

CAUSALITY - OZONE

In the final 2013 ISA, EPA states that respiratory morbidity has a causal relationship with short-term O_3 exposures and a likely causal relationship with long-term exposures. Cardiovascular effects were likely to be causal following short-term exposures, and "suggestive of a causal relationship" following long-term exposures. Central nervous system effects were also "suggestive of a causal relationship" for all durations of exposure. Long-term exposure's effects on reproductive and developmental endpoints, including premature birth, low birth weight, and birth defects, are also suggestive of an association. However, the evidence for long-term exposures leading to cancer is not adequate to determine a relationship (U.S. EPA 2013).

CAUSALITY - NITROGEN DIOXIDE

In the External Review Draft of the 2015 ISA, EPA determined that there is a causal relationship between respiratory health endpoints and short-term NO_2 exposure (minutes to one month exposure duration). Long-term respiratory health effects (over one month to multiple year exposure duration) are deemed likely to be a causal relationship. Both of these statuses are updates from the last NO_2 ISA published in 2008, which stated that short-term respiratory effects were "sufficient to infer a likely causal relationship" and that long-term effects were "suggestive, but not sufficient" to determine a relationship (U.S. EPA 2008, 2015).

EPA has also updated their understanding of the weight of the evidence for non-respiratory endpoints. Both short- and long-term NO_2 exposures are considered "suggestive, but not sufficient" for cardiovascular and metabolic effects; this designation was a change from the "inadequate" designation given in 2008. In the 2015 ISA, EPA considered birth outcomes to be "suggestive, but not sufficient" of an association. However, EPA determined that the related outcomes of fertility, reproduction, pregnancy, and post-natal development still do not have adequate evidence to understand potential associations. Finally, EPA changed the designation for cancer endpoints from "inadequate" to "suggestive, but not sufficient" for long-term NO_2 exposures (U.S. EPA 2008, 2015).

CAUSALITY - SULFUR DIOXIDE

EPA reported in its 2008 ISA for sulfur oxides that epidemiologic studies show evidence of respiratory symptoms in children, especially children with underlying respiratory diseases such as asthma. It determined that there is a causal relationship between short-term SO_2 exposures and respiratory morbidity. However, EPA determined that there is "inadequate" evidence for long-term exposures to SO_2 leading to respiratory morbidity. For cardiovascular morbidity and short-term SO_2 exposures, EPA reports that the available literature is not adequate to determine a relationship (U.S. EPA 2008).

RESPIRATORY HOSPITAL ADMISSIONS

STUDIES FROM U.S. EPA RIAS

All three RIAs assess the impacts of air pollutants on respiratory hospital admissions. The O_3 and SO_2 RIAs quantify all respiratory hospital admissions, using results from Katsouyanni et al. (2009) and Schwartz et al. (1996), respectively. The NO_2 RIA does not quantify impacts from all respiratory admissions but instead, it calculates the change in hospital admissions only for asthma (Linn et al. 2000) and chronic obstructive pulmonary disease (COPD) causes (Moolgavkar 2003).

- **Katsouyanni et al. (2009)** is a multi-country assessment of the impact of air pollutant on mortality and morbidity (90 U.S. cities, 32 European cities, and 12 Canadian cities). It reports U.S.-specific results for respiratory and cardiovascular morbidity and mortality and uses pollution data from U.S. EPA's Aerometric Information Retrieval System and AirData System (Air Quality System) for all criteria pollutants except lead. To prevent double counting, authors calculate total (rather than disease-specific) respiratory hospital admissions in the summer season for individuals ages 65-99. This publication reports 1-hour maximum O_3 effect estimates, which EPA converted to 8-hour maximum effect estimates to match their analysis in the 2014 O_3 RIA. EPA used equal-weight averaging to pool results of natural and penalized splines models. EPA only relied on results from the single-pollutant O_3 model because the multiple pollutant models were for the full year.

- **Schwartz et al. (1996)** is a review paper using an example of an elderly population in Cleveland, OH. Data were collected in 1988-1990. Because of the location of this study and the availability of newer studies, we do not recommend the use of this publication in SCAQ's assessment.

- **Linn et al. (2000)** regressed the rate of hospital admissions for asthma on same day exposures to NO_2 (daily average) for populations 0-29 years and 30-99 years in Los Angeles.

- **Moolgavkar (2003)** calculated the impact of daily NO_2 averages on COPD hospital admissions in Los Angeles and Cook counties. This study used lags of 0-5 days and focused only on those 65 years or older. The strongest association was seen with a daily lag of 0 (i.e., the same day). We believe assessing the impact of specific respiratory diseases in elderly adults may lead to a strong risk of double counting HA when combined with studies that provide C-R functions for all respiratory HA.

STUDIES FROM LITERATURE REVIEW: ALL RESPIRATORY HOSPITAL ADMISSIONS

- **Karr et al. (2007)** assessed the effects of $PM_{2.5}$, NO_2, CO, O_3 exposure on severe bronchiolitis on infants three weeks to one year. This study measured 18,595 hospital discharges in the South Coast Air Basin and matched each case to 10 controls (169,472) based on age and gestational age. Authors assigned monitoring

stations by ZIP code, and controlled for weather (humidity and temperature), and sociodemographic factors. Authors measured exposure both by mean lifetime expo sure (mean of monthly averages) and by mean concentrations the month before admission (average of daily levels over the month). However, in single pollutant models, $PM_{2.5}$ was the only pollutant significantly associated with bronchiolitis.

- **Rodopoulou et al. (2014)** studied respiratory and cardiovascular HA and ED visits associated with PM_{10}, $PM_{2.5}$, and O_3 in adults (18 years or older) in Doña Ana County New Mexico. Exposure data came from three monitoring stations in the study area. The paper controlled for sex, age, and race/ethnicity. The mean 8-hour maximum O_3 was 43.2 ppbv. However, the study did not find significant associations with 10ppv increase in maximum O_3 on the previous day. Additionally, authors note that windblown dust and fires are the source of much of the pollution in this area. These sources of air pollution may make this study less transferrable to other areas of the country.

STUDIES FROM LITERATURE REVIEW: ASTHMA-RELATED HOSPITAL ADMISSIONS

NO$_2$

- **Delfino et al.** (**2014)** assessed asthma-related hospital encounters (HA and ED visits) in a case-crossover study of over 11,000 children ages 0-18 years in Orange County, CA. This study measured $PM_{2.5}$, UFP, NO_X, and CO exposures at 1, 3, 5, and 7 day lags. The mean NO_2 concentrations were 26.6 ppb in the warm season and 16.1 ppb in the cool season. NO_2 and NO_X were significantly associated with these health endpoints only with 5- and 7-day lags. Less evidence exists on the biological plausibility of longer lag periods for acute effects of air pollution (e.g., see Roy et al. 2014).

- **Delamater et al**. **(2012)** is an ecological study of asthma hospitalizations in Los Angeles County. Authors developed a kriging model based on monitor data in Los Angeles to estimate exposures within 3 km x 3 km grid cells. They used data from OSHPD and interpolated annual state population data to calculate the average daily hospitalization rate by month. The study found that a one percent change in monthly average NO_2 was associated with a 0.37% (95% critical interval=0.22, 0.52) increase in hospitalizations.

Ozone

- **Meng et al. (2009)** analyzed the effects of annual average of O_3, $PM_{2.5}$, and PM_{10} exposures on asthmatics (all ages) in the San Joaquin Valley in CA, using California Health Interview Survey data. The two endpoints assessed were 1) experiencing daily or weekly symptoms in the past year and 2) asthma-related HA or ED visit in the past year. Exposure was measured from monitors within a five mile radius of residence of 1,502 participants. Authors calculated the annual average concentration from hourly measurements of O_3. The study adjusted for

age, gender, race, and poverty; smoking was assessed but not included in the final model. In the year prior to the study, the odds ratio of an asthma-related ED visit or hospital admission was 1.49 (95%: 1.05, 2.11) per 10 ppb annual average increase of O_3.

- **Moore et al. (2008**) analyzed the relationship between warm season O_3 concentrations and hospital discharges in children (birth-19 years) over a period of 18 years in the South Coast Air Basin. This region is home to about 4 million children. Authors developed a 10km x 10km grid over the study area. To each grid cell, they assigned ZIP-level hospital discharge data, quarterly average O_3, SO_2, NO_2, CO, and PM_{10} concentrations, and demographic data from the 1980, 1990, and 2000 U.S. Census (smallest area available). O_3 decreased over the course of the study. Every 10ppb increase in the mean quarterly 1-hour maximum O_3 above the median value of 87.7ppb was associated with a 4.6% increase in hospital discharges. This study controlled for race, income, temperature, humidity, income, and birth location.

RECOMMENDATION

Based on our assessment of EPA's most recent NAAQS RIAs and our literature review on respiratory HA, we recommend SCAQMD use two studies in their assessment of O_3 effects: Katsouyanni et al. (2009) for all respiratory HA in individuals ages 65-99 years and Moore et al. (2008) for asthma HA in children. Katsouyanni et al. provides the most comprehensive assessment of total respiratory HA across the U.S. and is the only study chosen by U.S. EPA to calculate O_3-related respiratory HA estimates. We do not recommend including studies that assessed disease-specific endpoints in individuals 65-99 years, as this set up would lead to double counting the effects of exposure (i.e., Delamater et al., Moolgavkar et al.).

To include the effect of O_3 exposure on children's asthma-related HA, we recommend the C-R function from Moore et al. (2008). This study includes individuals from birth to 19 years and thus does not overlap with the population assessed in Katsouyanni et al.

Because NO_2 is often a marker of traffic-related air pollution and is often highly correlated with $PM_{2.5}$ exposures near roadways (Beckerman et al. 2007), we do not recommend that SCAQMD assess asthma-related hospital admissions separately for NO_2. In our PM report, we recommended the use of Delfino et al. (2014) for asthma-related HA and ED visits. Using the reported C-R functions for both $PM_{2.5}$ and NO_2 may lead to double counting of the same cases.

RESPIRATORY ED VISITS

For all three pollutants, EPA quantified the impacts to asthma-related ED visits. EPA chose to focus on asthma as it does not have an economic valuation function for ED visits for all respiratory causes. As presented in Exhibit 3, EPA pooled multiple studies in each RIA using random effects pooling. However, the majority of these studies assessed populations in the eastern U.S.: Atlanta (Peel et al., Sarnat et al.), New York (Ito et al.,

New York State Department of Health), Pittsburgh (Glad et al. 2012), Portland, ME (Wilson et al.) or in Hawai'i (Michaud 2004). Only Mar and Koenig (2009) analyzed a population living the western U.S. (Seattle). Studies in the east coast may not accurately reflect pollution patterns in southern California. For the study based in Hawai'i, SO_2 was used to measure "vog" (volcanic fog). This phenomenon is not found in the study area.

STUDIES FROM LITERATURE REVIEW: RESPIRATORY ED VISITS

Ozone studies

- **Mar and Koenig (2009)** studied the effects of O_3 and $PM_{2.5}$ exposures on asthma-related ED visits for adults and children (<18 years) in Seattle. O_3 data from May-October came from two stations; $PM_{2.5}$ data came from three stations. Over the four years of study, 1-hour maximum O_3 was 39 ppb and 8-hour maximum was 32 ppb. This paper did not control for potentially confounding factors (demographics, smoking, etc.); however authors state controlling for these factors was not necessary as they do not change over the several day lag between exposure and response. Authors did not find an association with $PM_{2.5}$ but did find the following results for a 10ppb increase in O_3:

  - Children, same day:

    - Maximum daily average O_3 concentrations; RR 1.10 (95% CI: 1.02-1.18)

    - Maximum 8-hour 1.11 (95% CI: 1.01-1.19)

  - Children, three day lag:

    - Maximum daily average O_3 concentrations; RR 1.08 (95% CI: 1.00-1.18)

    - Maximum 8-hour 1.11 (95% CI: 1.02-1.21)

    - Similar results for 2 and 4 day lags.

  - Significant, but smaller associations for adults:

    - Lags of 4-5 days significant for 1-hour maximum

    - Lags of 2, 4, 5 days significant for 8ihour maximum

- **Meng et al. (2009)** assessed the effects of ozone exposure on asthma-related ED visits; see description above for further information.

RECOMMENDATIONS

We recommend that SCAQMD use Mar and Koenig to assess the impact of O_3 exposure on asthma-related ED visits in southern California. This study assessed both adults and children, was located in the western U.S., and was included in the EPA RIA for O_3. The concentration-response selected from this study is an 11% increase in asthma-related ED visits for each 10ppb increase in O_3 (95% CI: 1.01-1.19) based on the 8-hour maximum

O$_3$ concentration. While this study does not assess populations in California, it does analyze a west coast city (Seattle), which is likely to have more similar air pollution composition to the Los Angeles region than cities in the eastern part of the U.S. We did not find studies that show a clear relationship between NO$_2$ and SO$_2$ exposures and this outcome.

ASTHMA EXACERBATION

All three RIAs assessed the effect of asthma exacerbation in children. This endpoint is defined as worsening symptoms of asthma, including wheeze, cough, medication usage, and/or asthma exacerbation (attack), as indicated in some research on the use of unscheduled rescue medications. EPA did not separately quantify this endpoint for adults because EPA assumed adult asthma exacerbation effects are accounted for in work loss days and minor restricted activity days. The O$_3$ RIA used equal weight pooling for Mortimer et al. (2002), O'Connor et al. (2008), and Schildcrout et al. (2006). The NO$_2$ RIA used random/fixed effects pooling for ages 4-12 years for O'Connor et al., Schildcrout et al., and Ostro et al. (2001) and then summed these results with the results of Delfino to include 13-18 year olds. Based on findings from a U.S. EPA Scientific Advisory Board (SAB-HES (2004)) and the National Research Council (NRC 2002), EPA decided to apply the effect estimates to ages 6-18, regardless of the specific population included in individual studies.

- Although **Delfino et al. (2002)** analyzed participants in southern California, the small sample size of 22 leads us to recommend pooling this result with other larger studies.

- **Mortimer et al. (2002)** studied 846 asthmatic children ages 4-9 years from the National Cooperative Inner-City Asthma Study involving eight U.S. cities: New York; Baltimore; Washington, DC; Detroit; Cleveland; Chicago; and St. Louis. The study assessed areas with at least 30% of residents below the federal poverty line and measured asthma symptoms and lung function. Pollution measures (O$_3$, SO$_2$, NO$_2$, PM$_{10}$) came from U.S. EPA's Aerometric Information Retrieval System. In single pollutant models:

  - O$_3$: OR per IQR four day average, 1.16 (95% CI: 1.02, 1.30)

  - SO$_2$: 1.32 (95% CI: 1.03, 1.70) per IQR two day average

  - NO$_2$: 1.48 (95% CI: 1.02, 2.16) per IQR six day average

- **O'Connor et al. (2008)** followed 861 children ages 5-12 years with persistent asthma and atopy from low-income Census tracts in Boston, the Bronx, Chicago, Dallas, New York, Seattle, and Tucson. For two weeks every six months, participants kept a journal where they recorded lung function, symptoms (wheeze/cough days, nighttime asthma, slow play, missed school days per two week period) and missed school days. Pollution concentrations were pulled from U.S. EPA's Aerometric Information Retrieval System; the median distance to monitors was 2.3km. About half of the children lived with adult smoker. In

single pollutant models, O_3 and SO_2 were not significantly associated with symptoms. NO_2 was significant for nighttime asthma, slow play, and missed school over two week periods. The odds ratios for the 10th to 90th percentile change (20.4 ppb NO_2) were:

- o Nighttime asthma: 1.37 (95% CI: 1.08, 1.73)

- o Slow play: 1.26 (95% CI: 1.04, 1.54)

- o Missed school: 1.67 (95% CI: 1.18, 2.36)

- **Schildcrout et al. (2006)** analyzed daily symptoms and rescue inhaler use over the warm season in 990 children in eight North American cities (Albuquerque, Baltimore, Boston, Denver, San Diego, Seattle, St. Louis, Toronto) over two years as part of the Childhood Asthma Management Program. This study assessed short-term exposures to SO_2, PM_{10}, and O_3, with exposure-response lags of up to two days. The authors used monitor data from U.S. EPA's Aerometric Retrieval System and Environment Canada. The study controlled for race/ethnicity, annual family income, age, and sensitivity to rescue meds. O_3 (1-hour maximum) was not significant for any lag. For increases of 20 ppb for NO_2 (24 hour average):

  - o NO_2 odds ratios: 1.09 (95% CI: 1.03, 1.15) for 2 day lag; 1.06 (95% CI: 1.0, 1.13) same day; 1.04 (95% CI: 1.01, 1.07) 3 day moving sum

  - o NO_2 rate ratio for use of rescue inhaler: 1.05 (95% CI:1.01, 1.09) for 2 day lag

  - o SO_2: 1.04 (95% CI: 1.00, 1.08) 3 day moving sum

- **Ostro et al. (2001**) studied the risk of asthma exacerbation and air pollution exposure for 138 African-American children (8-13 years) with doctor-diagnosed asthma in central Los Angeles. The study lasted for 13 weeks. The study included PM_{10}, $PM_{2.5}$, NO_2, and O_3 and controlled for age, income, time trends, and temperature. Subjects completed a daily diary, including symptoms, medication usage, and lung function measurements. Asthma exacerbation was defined as "probability of a day with symptoms" and "onset of symptom episodes." Wheeze incidence (1.08 (95% CI: 1.02, 1.15) and wheeze prevalence (1.13 (95% CI: 1.04, 1.24) were associated with an increase of 5pphm in 1-hour maximum NO_2; no endpoints were associated with O_3. No pollutants were associated with additional medication usage in the full study population.

STUDIES FROM LITERATURE REVIEW: ASTHMA EXACERBATION

Ozone studies

- **Akinbami et al. (2010**) analyzed the effect of annual NO_2, SO_2, O_3, $PM_{2.5}$, and PM_{10} averages by county across the U.S. on asthma attack risk and asthma prevalence in children ages 3-17. Authors used the 2001-2004 National Health

Interview Survey (n=34,073). Pollution data came from the U.S. EPA Aerometric Information Retrieval System (AIRS). Twenty-four hour measurements for all pollutants were averaged quarterly, except O_3, which was averaged quarterly using the 8-hour maximum. Quarterly averages were then averaged to obtain rolling annual averages. Model was adjusted for presence of adult smoker, race, education, age, sex, poverty, region, and single parent household. This study found no association with NO_2 or SO_2 in adjusted models. For every 5 ppb increase in O_3, the odds ratio for asthma attack in the previous year was 1.07 (95% CI: 1.00, 1.13).

- In addition to HA and ED visits, **Meng et al. (2009)** also analyzed the effects of annual average of O_3, $PM_{2.5}$, and PM_{10} exposures asthma exacerbation. In the year prior to the study, the odds ratio for daily or weekly asthma symptoms (coughing, wheezing, shortness of breath, chest tightness, phlegm) was 1.23 (95%: 0.94, 1.60) per 10 ppb of O_3.

- **Meng et al. (2009)** assessed the effects of traffic density, and annual averages of O_3, CO, NO_2, $PM_{2.5}$, and PM_{10} on the risk of poorly controlled asthma in adults in Los Angeles and San Diego counties. Pollution concentration data was obtained from monitoring stations within a five mile radius of residence. This paper used the California Health Interview Survey data. Authors defined poorly controlled asthma as daily or weekly symptoms (coughing, wheezing, shortness of breath, chest tightness, phlegm) or two or more HA or ED visits in the prior year. This paper reported the percent of current smokers (18.6%) but does not adjust for smoking in the model. Authors found no association with NO_2, $PM_{2.5}$, or CO. Poorly controlled asthma was associated with higher O_3 exposure only in men and elderly individuals. Per 1pphm increase in O_3, the risk of poorly controlled asthma was 1.70 (95% CI: 0.91-3.18) in the elderly and 1.76 (95% CI: 1.05-2.94) in men.

- **Young et al. (2014)** investigated the association between $PM_{2.5}$ exposure and the incidence of doctor-diagnosed asthma, and self-reported wheeze and chronic cough in adult women ($\geq$ 35 years) without symptoms or asthma diagnoses at the start of the study. Study participants were from the nationwide, 50,884 subject Sister Study, a cohort of women with one sister diagnosed with breast cancer but who do not have the disease themselves. NO_2 exposure estimates were based on a national kriging and land-use regression model for the year 2006. For each interquartile range of NO_2 (5.8 ppb), the odds of wheeze in the fully adjusted model were 1.08 (95% CI: 1.00-1.17). Other asthma symptom endpoints were not significant. Authors controlled for age, body mass index, race, education, occupational exposures, smoking, health insurance, and fiber consumption.

RECOMMENDATIONS

We recommend that SCAQMD use the same set of studies as the EPA NO_2 NAAQS RIA to assess the impact of air pollution exposures on asthma exacerbation in children under 18 years. EPA pooled effect estimates from O'Connor et al. (2008); Ostro et al. (2001);

Schildcrout et al. (2006); and Delfino et al. (2002). We believe this approach provides a reasonable combination of studies that assessed this impact in the Los Angeles area with larger multi-city studies that included locations in the western U.S. We do not recommend that SCAQMD conduct a separate analysis of the effects of O_3 on this endpoint in order to avoid double counting.

ACUTE RESPIRATORY SYMPTOMS

In the 2014 O_3 RIA, EPA uses minor restricted activity days (MRAD) as the metric to account for acute respiratory symptoms. EPA relies on results from **Ostro and Rothschild (1989)**, which is the same study as in 2008 O_3 RIA. Ostro and Rothschild assessed 50,000 participants in the National Health Interview Survey, ages 18-65 years. This survey relies on participants' two week recall of their health status, which EPA notes may introduce a fair amount of error. The study controlled for age, sex, race, education, income, season, marital status, chronic health issue, and temperature. It did not control for smoking, but did not find a significant association between smoking status and air pollution. Previous studies have shown that not controlling for smoking does not necessarily bias the results. Exposures were taken from U.S. EPA's SAROAD monitors (O_3, $PM_{2.5}$). Weighting by the inverse of variance leads to a pooled estimate of MRAD of 0.185% for O_3 per 1 µg pollutant.

Schwartz et al. (1994) assessed respiratory illness in 1,844 children ages 7-14 years in six U.S. cities (Watertown, MA; Kingston-Harriman, TN; St. Louis, MO; Steubenville, OH; Portage, WI; and Topeka, KS) in the warm months. In single pollutant models, exposure to $PM_{2.5}$, NO_2 (1.27 (95% CI: 1.04, 1.56) per 10ppb increase), and O_3 (1.23 (95% CI: 0.99, 1.54) per 30 ppb increase) were associated with incidence of cough and SO_2 was associated with lower respiratory symptoms (1.28 (95% CI: 1.13, 1.46) per 10 ppb increase).

RECOMMENDATION

We recommend that SCAQMD continue to follow EPA's guidance on using MRADs to assess acute respiratory symptoms for O_3 (Ostro and Rothschild). In BenMAP, EPA provides the following C-R function for the 8-hour maximum O_3 concentration:

- (1-(1/EXP(Beta*DELTAQ)))*A*POP

    - Beta=0.002596

    - A= 0.02137 (MRAD for ages 18 to 64)

    - DeltaQ=Difference between baseline and control scenarios for the number of acute respiratory symptoms

SCHOOL LOST DAYS

Only the 2014 O_3 RIA assessed missed days of schools. Based on recommendations from the National Research Council (NRC 2002), EPA applied the random effects pooled

estimates from Gilliland et al. (2001) and Chen et al. (2000) to children 5-17 years. These studies are the same as used in the 2008 O_3 RIA.

- **Gilliland et al. (2001)** calculated the incidence of periods of absence from school associated with air pollution exposures in 2,081 fourth graders in communities within 200 miles of Los Angeles over 10 years. One central monitor in each of 12 communities measured O_3, NO_2, and PM_{10}. Hourly O_3 measurements were averaged over the eight hours between 10am and 6pm. Authors assessed smoking exposure, medical conditions, demographics, and outdoor activity level. EPA converted incidence to daily rates (absence periods x average duration) leading to 1.6 days for each period of absence. This study reports that short-term increases in O_3 were associated with school absences. No association was seen with NO_2 and PM_{10}. For each 20 ppb increase in O_3:

  - Illness-related absences increased 62.9% (95% CI: 18.4, 124.1%)

  - Respiratory illness: 82.9% (95% CI: 3.9, 222.0%)

  - Upper respiratory illnesses: 45.1% (95% CI: 21.3, 73.7%)

  - Lower respiratory illnesses with wet cough: 173.9% (95% CI: 91., 292.3%)

- **Chen et al. (2000)** similarly assessed daily rates of absence in Washoe County, Nevada, at 57 elementary schools encompassing nearly 28,000 students. Data on PM_{10}, O_3, and CO was taken from seven monitoring stations. The average O_3 concentration was 37.5ppb. The study controlled for weather and other confounders and found for each 50ppb increase in O_3, school absences increased by 13.01% (95% CI: 3.41-22.61%).

RECOMMENDATION

Because Gilliland et al. assesses missed school days in the South Coast Air Basin region, we recommend using the C-R function from Gilliland et al. as currently used in BenMAP for the 8-hour maximum O_3 concentration:

- (1-(1/EXP(Beta*DELTAQ)))*Incidence*POP*A*B

  - Beta = 0.007824

  - A= Scalar for % of school days in ozone season (0.3929)

  - B= Population of school children at-risk for a new absence (0.945)

  - DeltaQ=Difference between baseline and control scenarios for the number of school absences

NEW ENDPOINTS

This review found studies on multiple health endpoints not previously quantified by U.S. EPA. These include autism, asthma incidence, birth weight, birth defects, cardiovascular disease, diabetes, hypertension, respiratory ED visits, rheumatoid arthritis, and stroke.

IEc

For studies reported no association with air pollutants assessed. Of these new endpoints, we recommend the addition of new asthma disease incidence to the 2016 Socioeconomic Report. The remaining endpoints lack sufficient data to establish causality between exposure and morbidity. Below, we summarize our findings on studies of these endpoints in California, the western U.S., or nationwide.

NEW ASTHMA DISEASE INCIDENCE

This review found three articles on asthma incidence in California, one in Texas, and one nationwide. Wendt et al. (2014) assessed the effects of O_3, NO_2, and $PM_{2.5}$ in children in Harris County, Texas. Because we found similar studies that focus on southern California, we suggest SCAQMD use area-specific studies. The one nationwide study (Young et al., 2014) was the first publication to find an association with air pollution and asthma incidence in adult women. Because of the lack of supporting studies, we recommend that SCAQMD focus on asthma incidence in children only.

- **Islam et al. (2007)** followed 2,057 children 9-10 years without asthma or wheeze for eight years in southern California. Authors assessed exposure to O_3 and a "non-ozone package" consisting of NO_2, $PM_{2.5}$ and PM_{10}, acid vapor, elemental carbon, and organic carbon in "high" (90th percentile) and "low" (10th percentile) communities. The study assessed lung function changes. Over the course of the study, 212 cases of asthma developed. However, authors found no significant difference between high and low concentration O_3 communities for asthma incidence.

- **McConnell et al. (2010)** assessed the impact of exposures of traffic related air pollution (TRAP), NO_2, O_3 (8-hour average), PM_{10}, and $PM_{2.5}$ on doctor-diagnosed, new onset asthma in a cohort of nearly 2,500 kindergarten and first grade students followed for three years. TRAP was defined as distance to nearest freeway or major road and traffic density within 150m of a student's residence and school. Students were free from asthma or wheeze at the start of the study. Pollution was measured at a single monitor in each community and weather (temperature and humidity) assessed. The study population was from Southern California Children's Health Study. For the single pollutant NO_2 model, the study reported a hazard ratio of 2.17 (95% CI: 1.18-4.00) for a range of NO_2 exposure of 23.6ppb. Mean NO_2 was 20.4ppb, with a range of 8.7-32.3ppb and an interquartile range of 12.8ppb. However, the effects of NO_2 were attenuated when assessed with a multipollutant model with both TRAP and NO_2. O_3 and PM were not associated with asthma incidence. Authors found higher incidence of asthma in those children with higher rates in maternal smoking during pregnancy, history of allergies, and/or family history of asthma.

- **Nishimura et al. (2013)** analyzed early-life (first year) NO_2 exposure in 4,320 Latino and African American children ages 8 to 21 who were part of the GALA II and SAGE II studies. The former is a study on Latinos from Chicago, the Bronx, Houston, the San Francisco Bay area, and Puerto Rico) and the latter included

African Americans from the San Francisco Bay area. Authors calculated average annual exposures to NO_2, SO_2, PM_{10}, $PM_{2.5}$, and O_3 for each year of life based on U.S. EPA's Air Quality System. The study controlled for family history of asthma, IgE (high/low), and sex. Over all geographic areas in the study, NO_2 exposure during the first year of life and the first three years of life was associated with onset of asthma (OR of 1.17 (95% CI: 1.04, 1.31) and OR of 1.26 (95%: 1.07, 1.48), respectively) per 5ppb increase. The mean NO_2 concentration over the study was 19.3 ppb.

Recommendation

We recommend that SCAQMD use McConnell et al. to assess the impact of NO_2 exposures on the incidence of new asthma disease in children, using the following C-R function: hazard ratio of 2.17 (95% CI: 1.18-4.00) for a range of NO_2 exposure of 23.6ppb. This study focused on a southern California-specific population and assessed factors such as family history of asthma and allergies and maternal smoking. Nishimura et al. analyzed exposures from multiple locations across the U.S. and the only city in California assessed was San Francisco. Islam et al.'s use of percentiles rather than incremental changes and their combination of NO_2 with other air pollutants makes this study less ideal for assessing the impact of specific air pollutions on asthma incidence.

AUTISM

- **Becerra et al. (2013)** assessed the impact of $PM_{2.5}$, O_3, CO, NO and NO_2 exposure on the odds of developing autism for children living in Los Angeles. This study included 7,603 cases which were matched with 10 controls per case by sex, birth year, and gestational age. Exposure was measured via the nearest monitoring station and by two land-use regression models for NO_2. The first model estimated annual average pollutant concentrations and the second adjusted for each season. Results were adjusted by maternal age, education, race, maternal place of birth, type of birth, parity, insurance, and gestational age. For single pollutant models, the results were:

  - NO_2, annual average: 1.07 (95% CI: 1.03, 1.12); interquartile range of 5.41 ppb

  - NO_2, adjusted for seasons: 1.05 (95% CI: 0.98, 1.12); interquartile range of 9.70 ppb

  - NO_2, monitoring data: 1.04 (95% CI: 0.98, 1.10); interquartile range of 10.47 pbb

  - O_3, annual average: 1.06 (95% CI: 1.01, 1.12); interquartile range of 11.54 ppb

- **Volk et al. (2013)** conducted a case-control study on children enrolled in the Childhood Autism Risks from Genetics and the Environment (CHARGE) study in California. The study included 279 autistic children and 245 without autism. $PM_{2.5}$, PM_{10}, O_3, and NO_2 exposures were assessed from interpolating all monitor

data within 50 km of residence, with data from U.S. AQS and University of Southern California Children's Health Study. Ozone was not significantly associated with any outcome. For every 14.1 ppb increase in NO_2, the odds of having autism increased by 2.06 (95% CI: 1.37, 3.09) for exposures during the first year of life and by 1.81 (95% CI: 1.23, 2.65) for exposure during pregnancy. Stratifying outcomes by trimester led to odds ratios that were significant but smaller in magnitude. The model adjusted for sex, ethnicity, parental education, maternal age, and prenatal smoking. Risk did not change when population density and urban vs. rural areas were added to the model.

Recommendation

Despite the positive findings of these two studies, we do not recommend the use of autism as an endpoint in the 2016 Socioeconomic Report. Very few studies have reported on the association of autism and air pollutant exposures, and only limited data exists on the possible mechanism (Hertz-Picciotto et al. 2008). Because of the lack of data on the robustness of this association, we suggest that autism not be assessed in the 2016 report.

BIRTH DEFECTS

Gilboa et al. (2005) is a population-based case-control study investigating the association between maternal exposure to air pollutants (NO_2, O_3, SO_2) during weeks 3-8 of pregnancy and the risk of selected cardiac birth defects and oral clefts in livebirths and fetal deaths between 1997 and 2000 in seven Texas counties (n=5,338). When the highest quartile of exposure was compared with the lowest, the authors observed positive associations between SO_2 and isolated ventricular septal defects (odds ratio = 2.27, CI: 1.51, 3.09). There were inverse associations between ozone and isolated ventricular septal defects. Evidence that air pollution exposure influences the risk of oral clefts was limited. Suggestive results support a previously reported finding of an association between ozone exposure and pulmonary artery and valve defects.

Padula et al. (2014) looked at the association between environmental contaminants (7 ambient air pollutant and traffic exposures in California during the first two months of pregnancy, 1997-2006) and congenital anomalies (N=813 cases and N=828 controls). No change in risk of congenital heart defects were associated with NO_2 or O_3. There are some incongruities between this study and previous studies. Two previous studies reported an association between ozone and pulmonary artery value defects. The current study did not find positive associations of ozone with any heart defect grouping. The explanation for these discrepancies is unknown.

Stingone et al. (2014) investigated maternal exposures to air pollutants during weeks 2-8 of pregnancy and their associations with congenital heart defects in mothers from the National Birth Defects Prevention Study (a nine-state [including California] case control study). Positive associations were observed between exposure to NO_2 and coarctation of the aorta (OR = 2.5) and pulmonary valve stenosis (OR = 2.03). They also observed a positive association between SO_2 exposure and PVS, although it was attenuated at the

highest exposure level (OR=2.34). Associations between left ventricular outflow tract obstructions and NO_2 were supported by findings from the multipollutant analyses, although estimates were attenuated at the highest exposure levels.

Vinikoor-Imler et al. (2015) performed an exploratory analysis of ozone and fine particulate matter concentrations during early pregnancy and multiple types of birth defects on data from births in the Texas Birth Defects Registry and the National Birth Defects Prevention Study in Texas. Both databases had inverse associations between O_3 and septal heart defects as well as a positive association between O_3 and craniosynostosis in adjusted and co-pollutant models. To their knowledge, no other studies have reported on the relationship between O_3 concentrations and craniosynostosis. Multiple studies have been conducted examining the association between O_3 concentration and various heart defects. An earlier study performed in Texas also reported an inverse association between O_3 concentration and ventricular septal defects and null associations between O_3 concentrations and other cardiovascular defects. Further research needs to be done to fully understand the associations.

Zhu et al. (2015) studied criteria air pollutant exposure during three months preconception and gestational weeks 3-8 in relation to orofacial defects using data from the Consortium on Safe Labor (2002-2008). SO_2 was associated with isolated cleft lip with or without cleft palate (OR=1.93; CI: 1.16, 3.21). During gestational weeks 3-8, NOx were related to the risk for isolated cleft palate. Analyses by individual week revealed that positive associations of NOx with isolated cleft palate were most prominent from weeks 3-6 and 3-5 respectively. Exposure to several criteria air pollutants preconception and during early gestation was associated with elevated odds for isolated cleft palate while isolated cleft lip with or without cleft palate was only associated with preconception SO_2 exposure. According to Zhu et al., this study is the first time positive associations of exposure to NOx with isolated cleft palate and SO_2 with isolated cleft lip with or without cleft palate during the three months preconception exposure window, as a proxy of chronic exposure to air pollution.

Recommendation

While several of these birth defect studies find positive associations with gaseous air pollutants, we do not recommend adding this endpoint. These studies investigated a wide range of birth defects and it is unclear of these myriad endpoints have similar etiologies. These studies report contradictory findings. For example, Vinikoor-Imler et al. found positive associations with cardiac defects, whereas Padula et al. found none. Finally, the potential biological mechanism is not known.

BIRTH WEIGHT/PRETERM BIRTH

- **Laurent et al. (2014)** studied over 960,000 births in Los Angeles County and assessed exposure to NO_2 and O_3 via monitoring data from the California Air Resources Board. Hourly measurements were converted to daily means. For O_3, only measurements from 10 AM to 6 PM. Concentrations were then interpolated by a Bayesian kriging model. For exposures over an entire pregnancy, neither O_3

nor NO_2 was significantly associated with LBW (for an interquartile range (8.62 ppb) increase in O_3, the OR was 0.992 (95% CI: 0.984, 1.001); for and interquartile range (7.36 ppb) increase in NO_2, the OR was 1.008 (95% CI: 0.999, 1.017). This study controlled for many of the same factors as previously mentioned, although it did not control for smoking.

- **Morello-Frosch et al. (2010)** assessed over 3.5 million births over 10 years in California. Air pollution (CO, NO_2, O_3, SO_2, PM_{10}, $PM_{2.5}$, PM_{coarse}) was averaged by Census tract and ZIP code. Results are reported by monitor distances of 3, 5, and 10 km for both change in birth weight and odds of birth weight under 2,500g.

- For multivariate models using a distance of 3km, authors found a decrease in birth weight of 98.3g (95% CI: 7.0, 9.6) per 1 pphm NO_2 and a decrease of 8.9g (95% CI: 7.1, 10.6) per 1 pphm of O_3 for full-term births (>37 weeks). NO_2 slightly increased the odds of birth weight below 2,500g (OR of 1.03 (95% CI: 1.01, 1.05) per ppb; SO_2 had similar associations, but was only significant at 10km distance1.01 (95% CI: 1.00, 1.02) per ppb. The model controlled for sex, gestational age, season, year of birth, parity, and maternal race/ethnicity, education, marital status, prenatal care, birth place, and age. Authors state a decrease of this magnitude is unlikely to affect the health of an individual infant, but could have population-level impacts due to the widespread exposure to air pollutants across California.

- **Ritz et al., (2007)** conducted a case-control study of about 58,000 births in Los Angeles County to assess the effect of air pollution exposure on the risk of preterm birth. About 2,500 mothers were interviewed to assess confounders. Air pollution exposure was based on ZIP code. For women exposed to average NO_2 between 2.62-3.12 (second quartile) pphm, odds of preterm birth increased 22% (95% CI 1.13, 1.31) (birth cohort) to 4% (95% CI 0.83, 1.30) (interviewed cohort). For concentrations above 3.13 pphm, OR was 1.09 (1.00, 1.19) (birth cohort) to non-significant for interviewed cohort. O_3 was not significantly associated with preterm birth. This study adjusted for mother's age, race, education, season, birth season, and parity and for the interviewed cohort, smoking, alcohol use, and marital status.

- **Symanski et al. (2015)** studied the relationship between preterm birth and mean 8-hour maximum O_3 exposure for each 4 week period of each pregnancy in Harris County, Texas. O_3 data came from local monitoring data. The study assessed exposure during pregnancy for mothers who had singleton births in the Houston area from 2005-2007 (n=152,214). Authors assessed potential confounders including smoking status, race/ethnicity, education, age, body mass index, prenatal care, parity, insurance, and participation in Women, Infants, and Children services. Authors found statistically significant associations with O_3 exposures. For a 10ppb increase in county-wide O_3, authors reported the following odds ratios for a give four week period of pregnancy:

- o Late preterm birth (33-36 weeks gestation)
    - Fifth 4-week period: OR=1.08 (95%CI: 1.04, 1.12)
    - Sixth: OR=1.05 (95% CI: 1.01, 1.09)
    - Seventh: OR=1.07 (95% CI: 1.03, 1.10)
  - o Moderate preterm birth (29-32 weeks gestation)
    - Fifth: OR=1.13 (95% CI: 1.02, 1.25)
    - Seventh: OR=1.15 (95% CI: 1.04, 1.27)
  - o Severe preterm birth (20-28 weeks gestation)
    - Fifth: OR=1.21 (95% CI: 1.08, 1.36).

- **Trasande et al. (2013)** assessed the impact of air pollutants on low birth weight across the U.S. This study used the Kids Inpatient Database (KID), which records in-hospital births from up to 38 states (depending on year). Authors used pollutant concentrations from the U.S. EPA Aerometric Information Retrieval System (AIRS) coupled with random subsampling of over 2.6 million births in KID for 2000, 2003, and 2006. Authors controlled for gestational age, birth month, gender, race, socioeconomic variables. They were able to link one third of births in KID to AIRS data (lead, PM_{10}, NO_2, SO_2, CO and $PM_{2.5}$, and reactive volatile organic compounds). Single pollutant models of NO_2 showed an association with odds of preterm birth (OR of 1.02 (95% CI of 1.01, 1.04)) and preterm LBW (OR of 1.26 (95% CI of 1.06, 1.50)). O_3 is associated with very LBW (OR of 2.60 (95% CI: 1.40, 4.82). In the multi-pollutant models, neither birth weight as a continuous variable nor as a categorical variable (i.e., <2,500g and <1,500g) showed significant associations with NO_2 or O_3.

Recommendation

Although there is a general coherence of associations between adverse impacts on infants and pre-birth air pollution exposure to the mother, because of the limited number of studies assessing birth weight and preterm birth, and the inconsistencies in the specific pollutant and exposure time of most effect, we do not yet recommend quantifying these endpoints to the 2016 Socioeconomic Report. Laurent et al. did not find statistically significant associations with low birth weight risk. Morello-Frosch et al. find small decreases in birth weight, but authors state that these small changes may not have any significant health impact. The upper range of their estimated decreases were under four tenths of an ounce. While Ritz et al., Symanski et al., and Trasande et al. all report significant associations with air pollutant exposures and preterm birth, their studies differ on most associated pollutant and when during pregnancy an exposure has the greatest impact.

IEc

- **Ensor et al. (2013)** assessed over 11,500 cases of out of hospital cardiac arrest in adults (18 years and over) in Houston, TX. Authors analyzed hourly and daily O_3, $PM_{2.5}$, NO_2, SO_2, and CO exposures and controlled for weather. Cardiac arrests were included in the study only if the patient was not dead on arrival, based on data from the Houston emergency services. Results were stratified by age, sex, race, and preexisting conditions. "A 20-ppb ozone increase for the 8-hour average daily maximum was associated with an increased risk of OHCA on the day of the event (1.039; 95% confidence interval, 1.005–1.073). Each 20-ppb increase in ozone in the previous 1 to 3 hours was associated with an increased risk of OHCA (1.044; 95% confidence interval, 1.004–1.085). Relative risk estimates were higher for men, blacks, or those aged >65 years."

- **Koken et al. (2013)** analyzed the effect of air pollution levels (PM_{10}, O_3, NO_2, SO_2, CO) and maximum daily temperature (Tmax) on daily HA for cardiovascular diseases in men and women ages 65 and older in July and August between 1993 and 1997 in Denver, Colorado. Unit of analysis was daily admissions >65 years old per 10,000 residents. The eligible population (>65 years) in Denver started at 64,000 at the beginning of the study and declined to 60,000 by the end. Admissions data for males and females (38% and 62%, respectively) for acute myocardial infarction (AMI), coronary atherosclerosis, pulmonary heart disease, cardiac dysrhythmias, and congestive heart failure were collected for a total of 310 days. Daily HA data were provided by the Agency for Healthcare Research and Quality (AHRQ; Rockville, MD) which maintains state-specific hospital discharge databases as part of the Healthcare Cost and Utilization Project (HCUP 2001). Air pollution data were extracted from the U.S. Environmental Protection Agency (EPA) Aerometric Information Retrieval System (AIRS) (U.S. EPA 2002). Daily concentrations of the U.S. EPA's criteria air pollutants were obtained from all of the monitoring stations in Denver County. Daily 24-hr meteorological measurements such as Tmax and DPT were provided by the National Climate Data Center (NCDC 2002). HA data was adjusted for yearly trends, day-of-week effects, ambient maximum temperature, and dew point temperature (DPT). To account for potential delays in disease incidence after exposures, lag times of 1–4 days for each of the environmental variables were included as additional model covariates. This study found a "marginal" positive association between SO_2 and cardiac dysrhythmias at lag day zero for males and females combined. An increase in the daily average level of SO_2 from the 25th percentile (3.8 ppb) to the 75th percentile (7.2 ppb) is associated with an increased risk of hospital admission for cardiac dysrhythmias of 8.9%, with a 95% CI of –0.34–18.93% (p = 0.055). Positive associations were also found between O_3 and some endpoints at various lag days (coronary atherosclerosis at lag day 2, and pulmonary heart disease at lag day 1), and a negative association was found between O_3 and AMI at lag day zero. No association was found between PM_{10} or NO_2 and any of the health outcomes.

- **Rodopoulou et al. (2014):** as noted above, this study did not find significant associations with cardiovascular HA and ED visits and O_3.

Recommendation

The association between $PM_{2.5}$ exposure and cardiovascular outcomes has been well-established, as discussed in our $PM_{2.5}$ report to SCAQMD. However, exposures to gaseous pollutants and cardiovascular morbidity are less well understood. Of the three studies detailed above, one (Rodopoulou et al.) found no association between exposure and cardiovascular endpoints. Koken et al. found several moderate associations, depending on the lag time used. However, as reported in Roy et al. (2014), cardiovascular effects from air pollution exposure are biologically more likely to occur at lags within several days. Ensor et al. analyzed emergency medical services data on out of hospital cardiac arrests, but because this paper states that nearly 90% of people who experience these cardiac arrests die, using the results of this paper may lead to double counting with mortality endpoints. Based on the limited amount of data on these associations, we recommend that SCAQMD continue to assess the effects of cardiovascular endpoints with $PM_{2.5}$ exposures, but not yet add gaseous effect estimates at this time.

HYPERTENSION AND DIABETES

Coogan et al., (2012) is a study of African American women in LA for incident hypertension and type II diabetes associated with exposure to $PM_{2.5}$ and NOx. The authors found a statistically significant association of both with NO_2 exposure. This was the first study of incident hypertension with air pollution and the third study to address diabetes incidence and air pollution.

Eze et al. (2015) conducted a review and meta-analysis of 13 studies in either Europe or North America of air pollutant exposure and type II diabetes risk. They found overall a positive association, but also identified a high risk of bias in results. A similar review by Balti et al. in 2014 also found a generally positive association of type II diabetes with NO_2 and $PM_{2.5.}$

Mobasher et al. (2013) evaluated the effects of ambient air pollution on the odd of hypertensive disorder of pregnancy and whether these associations varied by body mass index in a case-control study among 298 predominantly Hispanic women in the LA county area during 1996-2008. There was a significantly positive association between exposure to O_3 in the second trimester and hypertensive disorder of pregnancy (OR per 15ppb=2.05; CI: 1.22-3.46). While there are currently no studies investigating the role of O_3 in predisposing to hypertensive disorders of pregnancy, Liu et all showed a significant association between O_3 and Intrauterine growth restriction during the 2nd trimester of pregnancy. The exact mechanism by which ozone acts to increase risk is unknown; however, it is likely that increased levels of O_3 leads to increased lipid peroxidation, resulting in the release of pro-inflammatory cytokines into the circulation. Exposure to

NO$_2$ in any trimester was not significantly associated with hypertensive disorder of pregnancy. This is consistent with previous findings.

Robledo et al. (2015) looked at the impact of preconception and early pregnancy air pollution on gestational diabetes mellitus risk. Data from electronic medical records was obtained for 219,952 singleton deliveries without pregestational diabetes among women between 2002 and 2008 based in 12 clinical centers across 15 hospital referral regions. Preconception maternal exposure to NOx (RR=1.09, CI: 1.04, 1.13) and SO$_2$ (RR=1.05, 1.01, 1.09) were associated with increased risk of subsequent GDM and risk estimates remained elevated for first trimester exposure. Preconception O$_3$ was associated with lower risk of subsequent GDM (RR=0.93, 0.90, 0.96) but risks increased later in pregnancy. Findings for NO$_x$ were consistent with prior studies of GDM and air quality but they added new information on the preconception exposure window and have evaluated the association between GDM with all criteria pollutants, including constituents of PM$_{2.5}$. They identified novel associations between preconception SO$_2$ exposure and second trimester ozone exposure and increased GDM risk.

Recommendation

Our literature review found a limited number of studies on the link between exposures to air pollutants and chronic cardiovascular and metabolic diseases such as hypertension and type II diabetes. Our review finds suggestive new evidence for both of these endpoints, but literature findings are not yet sufficient to support quantification of these endpoints.

RHEMATOID ARTHRITIS

- **Hart et al. (2013)** examined whether long-term exposures to specific air pollutants were associated with rheumatoid arthritis risk among women in the Nurses' Health Study (n=111,425). Overall, they found no evidence of increased risks of RA, seronegative or seropositive RA, with exposure to the different pollutants (including SO$_2$ and NO$_2$), and little evidence of effect modification by socioeconomic status or smoking status, geographic region, or calendar period. While there were no consistent overall associations between air pollution and risk for RA, they did observe a suggestion that selected pollutants (NO$_2$ and SO$_2$) were associated with increased risk of RA.

Recommendation

We do not recommend adding rheumatoid arthritis as an endpoint. The one national study discovered during the literature review found no evidence that air pollutants are associated with the risk of development of arthritis.

STROKE

We identified two studies assessing the relationship between stroke and O$_3$, NOx, or SO$_2$: one found a borderline association with short term levels of PM and ozone and ischemic stroke risk in Corpus Christi, TX, a city with relatively low pollution levels. The other found a relationship across 9 US cities with Ischemic stroke only (not hemorrhagic) and

PM, NOx, and SO$_2$. We assess that these impacts are likely captured in our recommended C-R function for PM and ischemic stroke.

RECOMMENDATIONS SUMMARY

Exhibit 4 summarizes our recommended gaseous pollutants health endpoints for the 2016 Socioeconomic Report. In summary, we propose evaluation of the same endpoints evaluated in the 2014 EPA Ozone NAAQS RIA, 2010 EPA Nitrogen Dioxide NAAQS RIA, and 2010 EPA Sulfur Dioxide NAAQS RIA plus new cases of asthma in children under 18 years. We have changed several of the recommended studies from the NAAQS RIAs. Many of these changes involve using more locally relevant studies conducted in southern California. The EPA RIAs considered the entire U.S., whereas the focus of the 2016 Socioeconomic Report will be the South Coast Air Basin. Gray-highlighted rows indicate changes in recommended studies from the EPA NAAQS RIAs.

Note that all C-R functions and related parameters will be developed and applied in accordance with the EPA's BenMAP-CE User's Manual Appendix C (U.S. EPA, 2015). Specific functional forms and input parameters will be specified once study and risk model recommendations are finalized.

IEc

EXHIBIT 4.   RECOMMENDED HEALTH ENDPOINTS FOR GASEOUS POLLUTANTS

ENDPOINT	POLLUTANT	STUDY	STUDY POPULATION
Premature Mortality, Short-term Exposure			
Deaths, All-Cause	Ozone	Pooled estimate: Bell et al., 2005 (meta-analysis result for LA) Bell et al., 2005 (NMMAPS result for LA)	All ages
Hospital Admissions			
Respiratory, all	O_3 (8-hour max)	Katsouyanni et al. (2009)	65-99 years
Respiratory, asthma	O_3 (8-hour max)	Moore et al. (2008)	<18 years
Emergency Department Visits			
Respiratory, asthma	O_3 (8-hour max)	Mar and Koenig (2009); Meng et al. (2009)	<18 years
Other Health Endpoints			
Asthma incidence (new cases)	O_3 (8-hour max)	McConnell et al. (2010)	<18 years
School loss days	O_3 (8-hour max)	Gilliland et al. (2001)	5-17 years
Acute respiratory symptoms/Minor restricted-activity days	O_3 (8-hour max)	Ostro and Rothschild (1989)	18-65 years
Asthma exacerbation	NO_2	Pooled estimate: O'Connor et al. (2008); Ostro et al. (2001); Schildcrout et al. (2006)	4 - 12
		Delfino et al. (2002)	13 - 18
Acute respiratory symptoms	NO_2; SO_2	Schwartz et al. (1994)	7-14 years

IEc

REFERENCES

1. Akinbami, L.J., Lynch, C.D., Parker, J.D., Woodruff, T.J. (2010). The association between childhood asthma prevalence and monitored air pollutants in metropolitan areas, United States, 2011-2004. Environmental Research. 110(3): 294-301.

2. Balti, E.V., Echouffo-Tcheuqui, J.B., Yako, Y.Y., Kengne, A.P. (2014). Air pollution and risk of type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Research and Clinical Practice. 106(2): 161-172.

3. Becerra, T.A., Wilhelm, M., Olsen, J., Cockburn, M., Ritz, B. (2013). Ambient air pollution and autism in Los Angeles County, California. Environmental Health Perspectives. 121(3): 380-386.

4. Bell, M.L., McDermott, A., Zeger, S.L., Samet, J.M., Dominici, F. (2004). Ozone and short-term mortality in 95 US Urban Communities. JAMA. 292(19):2372-2378.

5. Bell, M.L., Dominici, F., Samet, M. (2005). A meta-analysis of time-series studies of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study. Epidemiology. 16(4): 436-445.

6. Bell, M.L., Kim, J.Y., Dominici, F. (2007). Potential confounding of particulate matter on the short-term association between ozone and mortality in multisite time-series studies. Environmental Health Perspectives. 115(11): 1591-1595.

7. Bell, M.L. and Dominici, F. (2008). Effect modification by community characteristics on the short-term effects of ozone exposure and mortality in 98 U.S. communities. American Journal of Epidemiology. 167(8):986-997.

8. Chen, L., Jennison, B.L., Yang, W., Omaye, S.T. (2000). Elementary school absenteeism and air pollution. Inhalation Toxicology. 12(11):997-1016.

9. Coogan, P.F., White, L.F., Jerrett, M. Brook, R.D., Su, J.G., Seto, E., Burnett, R., Palmer, J.R., Rosenberg, L. (2012). Air pollution and incidence of hypertension and diabetes mellitus in black women living in Los Angeles. Circulation. 125(6): 767-772.

10. Delamater, P.L., Finley, A.O., Banerjee, S. (2012). An analysis of asthma hospitalizations, air pollution, and weather conditions in Los Angeles County, California. Science of the Total Environment. 425:110-118.

11. Delfino, R.J., Zeiger, R.S., Seltzer, J.M., Street, D.H., McLaren, C.E. (2002). Association of asthma symptoms with peak particulate air pollution and effect modification by anti-inflammatory medication use. Environmental Health Perspectives. 110(10): A607-617.

12. Delfino, R.J., Wu, J., Tjoa, T., Gullesserian, S.K., Nickerson, B., Gillen, D.L. (2014). Asthma morbidity and ambient air pollution: Effect modification by residential traffic-related air pollution. Epidemiology. 25:48-57.

13. Dominici, F., Peng, R.D., Bell, M.L., et al. (2006). Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA. 295:1127-1134.

14. Ensor, K.B., Raun, L.H., Persse, D. (2013). A case-crossover analysis of out-of-hospital cardiac arrest and air pollution. Circulation. 127(11): 1192-1199.

15. Eze, I. C., Hemkens, L. G., Bucher, H. C., Hoffmann, B., Schindler, C., Künzli, N.,Probst-Hensch, N. M., et al. (2015). Association between Ambient Air Pollution and Diabetes Mellitus in Europe and North America: Systematic Review and Meta-Analysis. Environmental Health Perspectives. 123(5): 381–389. http://doi.org/10.1289/ehp.1307823

16. Franklin, M. and Schwartz, J. (2008). The impact of secondary particles on the association between ambient ozone and mortality. Environmental Health Perspective. 116(4): 453-458.

17. Gauderman, W.J., Urman, R., Avol, E., Berhane, K., McConnell, R., Rappaport, E., Chang, R., Lurmann, F., Gilliland, F. (2015). Association of improved air quality with lung development in children. New England Journal of Medicine. 372(10): 905-913.

18. Gilboa, S.M., Mendola, P., Olshan, A.F., Langlois, P.H., Savitz, D.A., Loomis, D., Herring, A.H., and Fixler, D.E. (2005). Relation between Ambient Air Quality and Selected Birth Defects, Seven County Study, Texas, 1997-2000. American Journal of Epidemiology. 162(3):238-252.

19. Gilliland, F.D., Berhane, K., Rappaport, E.B., Thomas, D.C., Avol, E., Gauderman, W.J., London, S.J., Margolis, H.G., McConnell, R., Islam, K.T., Peters, J.M. (2001). The effects of ambient air pollution on school absenteeism due to respiratory illnesses. Epidemiology. 12(1): 43-54.

20. Glad, J.A., Brink, L.L., Talbott, E.O., Lee, P.C., Xu, X., Saul, M., Rager, J. (2012). The relationship of ambient ozone and $PM_{2.5}$ levels and asthma emergency department visits: possible influence of gender and ethnicity. Environmental and Occupational Health. 67(2): 103-108.

21. Hao, Y., Balluz, L., Strosnider, H., Wen, X.J., Li, C., Qualters, J.R. (2015). Ozone, fine particulate matter, and chronic lower respiratory disease mortality in the United States. American Journal of Respiratory and Critical Care Medicine. 192(3):337-341.

22. Hart, J.E., Kallberg, H., Laden, F., Costenbader, K.H., Yanosky, J.D., Klareskog, L., Aldredsson, L., Karlson, E.W. (2013). Ambient air pollution exposures and

risk of rheumatoid arthritis in the Nurses' Health Study. Arthritis Care Research. 65(7): 1190-1196.

23. Agency for Healthcare Research and Quality (AHRQ). (2000). HCUPnet, Healthcare Cost and Utilization Project.

24. Hertz-Picciotto, I., Park, H-Y., Dostal, M., Kocan, A., Trnovec, T., Sram, R. (2008). Prenatal exposures to persistent and non-persistent organic compounds and effects on immune system development. Basic Clin Pharmacol Toxicol 102(2):146–154.

25. Huang, Y., Dominici, F., Bell, M.L. (2005). Bayesian hierarchical distributed lag models for summer ozone exposure and cardio-respiratory mortality. Environmetrics. 16: 547-562.

26. Islam, T., Gauderman, W.J., Berhane, K., McConnell, R., Avol, E., Peters, J.M., Gilliland, F.D. (2007). Relationship between air pollution, lung function and asthma in adolescents. Thorax. 62(11):957-963.

27. Ito, K., Thurston, G.D., Silverman, R.A. (2007). Characterization of $PM_{2.5}$, gaseous pollutants, and meteorological interactions in the context of time-series health effects models. Journal of exposure science and environmental epidemiology. Supp 2:S45-60.

28. Ito, K., De Leon, S.F., Lippmann, M. (2005). Associations between ozone and daily mortality. Epidemiology. 16(4): 446-457.

29. Jerrett, M., Burnett, R.T., Pope, C.A., Ito, K., Thurston, G., et al. (2009). New England Journal of Medicine. 360: 1085-1095.

30. Jerrett, M., Burnett, R.T., Beckerman, B.S., Turner, M.C., et al. (2013). Spatial analysis of air pollution and mortality in California. American Journal of Respiratory and Critical Care Medicine. 188(5): 593-599.

31. Karr, C., Lumley, T., Schreuder, A., Davis, R., Larson, T., Ritz, B., Kaufman, J. (2007). Effects of subchronic and chronic exposure to ambient air pollutants on infant bronchiolitis. American Journal of Epidemiology. 165(5): 553-560.

32. Katsouyanni, K. Samet, J.M. (2009). Air pollution and health: A European and North American approach. The Health Effects Institute. 142: 1-132.

33. Kokem P.J.M., Piver, W.T., Ye, F., Elixhauser, A., Olsen, L.M., Portier, C.J. (2013). Temperature, air pollution, and hospitalization for cardiovascular diseases among elderly people in Denver. Environmental Health Perspectives. 111(10): 1312-1317.

34. Kinney, P.L., Ito, K., Thurston, G.D. (1995). A sensitivity analysis of mortality/PM-10 associations in Los Angeles. Inhalation Toxicology. 7:59-69.

35. Krewski, D., Jerrett, M., Burnett, R.T., Ma, R., Hughes, E., Shi, Y., Turner, M.C., Pope, C.A., Thurston, G., Calle, E.E., Thun, M.J. (2009). Extended follow-up and

spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. Health Effects Institute. 140:1-154.

36. Laurent, O., Hu, J., Li, L., Cockburn, M., Escobedo, L., Kleeman, M.J., Wu, J. (2014). Sources and contents of air pollution affecting term low birth weight in Los Angeles County, California, 2001-2008. Environmental Research. 488-495.

37. Levy, J.I., Chemerynski, S.M., Sarnat, J.A. (2005). Ozone exposures and mortality: An Empiric Bayes metaregression analysis. Epidemiology. 16(4): 458-468.

38. Linn, W.S., Szlachcic, Y., Gong, H., Kinney, P.L., Berhane, K.T. (2000). Air pollution and daily hospital admissions in metropolitan Los Angeles. Environmental Health Perspectives. 108(5): 427-434.

39. Mar, T.F., Koenig, J.Q. (2009). Relationship between visits to emergency departments for asthma and ozone exposure in greater Seattle, Washington. Annuals of Allergy, Asthma, and Immunology. 103(6):474-479.

40. McConnell, R., Islam, T., Shankardass, K., Jerrett, M., Lurmann, F., Gilliland, F., Gauderman, J., Avol, E., Kunzli, N., Yao, L., Peters, J., Berhane, K. (2010). Childhood incident asthma and traffic-related air pollution at home and school. Environmental Health Perspectives. 118(7): 1021-1026.

41. Medina-Ramon, M., Schwartz, J. (2008). Who is more vulnerable to die from ozone air pollution. Epidemiology. 19(5):672-679.

42. Meng, Y.Y., Rull, R.P., Wilhelm, M., Lombardi, C., Balmes, J., Ritz, B. (2009). Outdoor air pollution and uncontrooled asthma in the San Joaquin Valley, California. Jounral of Epidemiology and Community Health. 64:142-147.

43. Meng, Y.Y., Rull, R.P., Wilhelm, M., Lombardi, C., Balmes, J., Ritz, B. (2010). Outdoor air pollution and uncontrolled asthma in the San Joaquin Valley, California. Journal of Epidemiology and Community Health. 64(2):142-147.

44. Michaud, J.P., Grove, J.S., Krupitsky, D. (2004). Emergency department visits and "vog"-related air quality in Hilo, Hawaii. Environmental Research. 95(1):11-19.

45. Mobasher, Z., Salam, M.T., Goodwin, T.M., Lurmann, F., Ingles, S.A., Wilson, M.L. (2013). Associations between ambient air pollution and hypertensive disorders of pregnancy. Environmental Research. 123:9-16.

46. Moogavkar, S.H. (2003). Air pollution and daily mortality in two U.S. counties: season-specific analyses and exposure-response relationships. Inhalation Toxicology. 15(9): 877-907.

47. Moolgavkar, S.H., McClellan, R.O., Dewanji, A., Turim, J. Luebeck, E.G. Edwards, M. (2013). Time-series analyses of air pollution and mortality in the

United States: A subsampling approach. Environmental Health Perspectives. 121(1): 73-78.

48. Moore, K., Neugebauer, R., Lurmann, F., Hall, J., Brajer, V., Alcorn, S., Tager, I. (2008). Ambient ozone concentrations cause increased hospitalizations for asthma in children: an 18-year study in Southern California. Environmental Health Perspectives. 116(8):1063-1070.

49. Morello-Frosch, R., Jesdale, B.M., Sadd, J.L., Pastor, M. (2010). Ambient air pollution exposure and full-term birth weight in California. Environmental Health Perspectives. 9(44):1-13.

50. Mortimer, K.M., Neas, L.M., Dockery, D.W., Redline, S., Tager, I.B. (2002). The effect of air pollution on innter-city children with asthma. European Respiratory Journal. 19:699-705.

51. National Agricultural Statistics Service (NASS). (2008). Maple Syrup- June 12, 2008: Maple syrup production up 30 percent nationalwide. U.S. Department of Agriculture, National Agricultural Statistics Service, New England Agricultural Statistics, Concord, NH.

52. National Research Council (NRC). (2002). Estimating the public health benefits of proposed air pollution regulations. Washington, DC: The National Academies Press.

53. Nishimura, K.K., Galanter, J.M., Roth, L.A., Oh, S.S., Thakur, N., et al. (2013). Early-life air pollution and asthma risk in minority children. American Journal of Respiratory and Critical Care Medicine. 188(3): 309-318.

54. New York Department of Health (NYDOH). (2006). A study of ambient air contaminants and asthma in New York City. New York State Department of Health Center for Environmental Health.

55. O'Connor, G.T., Neas, L., Vaughn, B., Kattan, M., Mitchell, H. (2008). Acute respiratory health effects of air pollution on children with asthma in US inner cities. Journal of Allergy and Clinical Immunology. 121(5): 1133-1139.

56. Ostro, B.D., Rothschild, S. (1989). Air pollution and acute respiratory morbidity: an observational study of multiple pollutants. Environmental Research. 50:238-247.

57. Ostro, B.D., Lipsett, M., Mann, J., Braxton-Owens, H., White, M. (2001). Air pollution and exacerbation of asthma in African-American children in Los Angeles. Epidemiology. 12(2): 200-208.

58. Ostro, B. Hu, Jianlin, Goldberg, D., Reynolds, P., Hertz, A., Bernstein, L., Kleeman, M.J. (2015). Associations of mortality with long-term exposures to fine and ultrafine particles, species and sources: Results from the California Teachers Study Cohort. Environmental Health Perspectives. 123(6): 549-556.

59. Padula, A.M., Tager, I.B., Carmichael, S.L., Hammond, S.K., Yang, W., Lurmann, F., Shaw, G.M. (2013). Ambient air pollution and traffic exposures and congenital heart defects in the San Joaquin Valley of California. Pediatric and Perinatal Epidemiology. 27(4): 329-339.

60. Peel, J.L., Tolbert, P.E., Klein, M., Metzger, K.B., Flanders, W.D., Todd, K., Mulholland, J.A., Ryan, P.B., Frumkin, H. (2005). Ambient air pollution and respiratory emergency department visits. Epidemiology. 16(2): 164-174.

61. Peng, R.D., Samoli, E., Pham, L., Dominici, F., Touloumi, G., Ramsay, T., et al. (2013). Air Quality Atmosphere and Health. 6(2): 445-453.

62. Ritz, B., Wilhelm, M., Hoggatt, K.J., Ghosh, J.K.C. (2007). Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. American Journal of Epidemiology. 166(9): 1045-1052.

63. Ritz, B., Wilhelm, M., and Zhao, Y. (2006). Air Pollution and Infant Death in Southern California 1989-2000. Pediatrics. 118(2):493-502.

64. Robledo, C.A., Mendola, P., Yeung, E. Mannisto, T., Sundaram, R., Liu, D., Ying, Q., Sherman, S., Grantz, K.L. (2015). Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus. Environmental Research. 137:316-322.

65. Rodopoulou, S., Chalbot, M.C., Samoli, E., DuBois, D.W., San Filippo, B.D., Kavouras, I.G. (2014). Air pollution and hospital emergency room and admissions for cardiovascular and respiratory diseases in Dona Ana County, New Mexico. Environmental Research. 129:39-46.

66. Roy, A., Gong, J., Thomas, D.C., Zhang, J., Kipen, H.M., et al. (2014). The cardiopulmonary effects of ambient air pollution and mechanistic pathways: a comparative hierarchical pathway analysis. PLoS One. 9(12): e114913.

67. Sarnat, J.A., Sarnat, S.E., Flanders, W.D., Chang, H.H., Mulholland, J., Baxter, L., Isakov, V., Ozkaynak, H. (2013). Spatiotemporally resolved air exchange rate as a modifier of acute air pollution-related morbidity in Atlanta. Journal of Exposure Science and Environmental Epidemiology. 23:606-615.

68. Schildcrout, J.S., Sheppard, L., Lumley, T., Slaughter, J.C., Koenig, J.Q., Shapiro, G.G. (2006). Ambient air pollution and asthma exacerbations in children: An eight-city analysis. American Journal of Epidemiology. 164(6): 505-517.

69. Schwartz, J., Dockery, D.W., Neas, L.M., Wypij, D., Ware, J.H., et al. (1994). Acute effects of summer air pollution on respiratory symptom reporting in children. American Journal of Respiratory and Critical Care Medicine. 150:1234-1242.

70. Schwartz, J., Spiz, C., Touloumi, G., Bacharova, L., et al. (1996). Methodological issues in studies of air pollution and daily counts of death or hospital admissions. Journal of Epidemiology and Community Health. 50(1):S3-S11.

71. Schwartz. (2005). How sensitive is the association between ozone and daily deaths to control for temperature. American Journal of Respiratory and Critical Care Medicine. 171:627-631.

72. Smith, K.R., Jerrett, M., Anderson, H.R., Burnett, R.T., et al. (2009). Public health benefits of strategies to reduce greenhouse-gas emissions: health implications of short-lived greenhouse pollutants. Lancet. 374(9707): 2091-2103.

73. Stingone, J.A., Luben, T.J., Daniels, J.L., Fuentes, M., Richardson, D.B., Aylsworth, A.S., et al. (2014). Maternal exposure to criteria air pollutants and congenital heart defects in offspring: results from the national birth defects prevention study. Environmental Health Perspectives. 122(8):863-872.

74. Symanski, E., McHugh, M.K., Zhang, X., Craft, E.S., Lai, D. (2015). Evaluating narrow windows of maternal exposure to ozone and preterm birth in a large urban area in Southeast Texas. Journal of exposure science and environmental epidemiology. 1-6.

75. Trasande, L., Wong, K., Roy, A., Savitz, D.A., Thurston, G. (2013). Exploring prenatal outdoor air pollution, birth outcomes and neonatal health care utilization in a nationally representative sample. Journal of Exposure Science and Environmental Epidemiology. 23(3):315-321.

76. U.S. EPA. (2004a). Advisory on plans for health effects analysis in the analytical plan for EPA's Second Prospective Analysis- Benefits and cots of the Clean Air Act, 1990-2020.

77. U.S. EPA. (2004b). Review of the Draft Analytical Plan for EPA's Second Prospective Analysis- Benefits and Costs of the Clean Air Act, 1990-2020: An advisory by the Advisory Council for Clean Air Compliance Analysis.

78. U.S. EPA (2004c). Advisory Council on Clean Air Compliance Analysis Response to Agency Request on Cessation Lag.

79. U.S. EPA. (2015). BenMAP-CE User Manual Appendices. Available at: http://www2.epa.gov/benmap/manual-and-appendices-benmap-ce. Accessed on September 23, 2015.

80. U.S. EPA. (2010). Final Regulatory Impact analysis (RIA) for the NO_2 National Ambient Air Quality Standards (NAAQS).

81. U.S. EPA. (2008). Integrated Science Assessment for Oxides of Nitrogen- Health Criteria.

82. U.S. EPA. (2015). Integrated Science Assessment for Oxides of Nitrogen- Health Criteria. External Review Draft.

83. U.S. EPA. (2008). Final Ozone NAAQS Regulatory Impact Analysis.

84. U.S. EPA. (2014). Regulatory Impact Analysis of the Proposed Revisions to the National Ambient Air Quality Standards for Ground-Level Ozone.

85. U.S. EPA. (2013). Integrated Science Assessment for ozone and related photochemical oxidants.

86. U.S. EPA. (2010). Final Regulatory Impact Analysis (RIA) for the SO_2 National Ambient Air Quality Standards (NAAQS).

87. U.S. EPA (2008). Integrated Science Assessment (ISA) for Sulfur Oxides- Health Criteria.

88. Vinikoor-Imler, L.C., Stewart, T.G., Luben, T.J., Davis, J.A., Langlois, P.H. (2015). An exploratory analysis of the relationship between ambient ozone and particulate matter concentrations during early pregnancy and selected birth defects in Texas. Environmental Pollution. 202:1-6.

89. Volk, H.E., Lurmann, F., Penfold, B., Hertz-Picciotto, I., McConnell, R. (2013). Traffic-related air pollution, particulate matter, and autism. JAMA. 70(1): 71-77.

90. Wendt, J.K., Symanski, E., Stock, T.H., Chan, W., Du, X.L. (2014). Association of short-term increases in ambient air pollution and timing of initial asthma diagnosis among Medicaid-enrolled children in a metropolitan area. Environmental Research. 131:50-58.

91. Wilson, A.M., Wake, C.P., Kelly, T., Salloway, J.C. (2005). Air pollution, weather, and respiratory emergency room visits in two northern New England cities: an ecological time-series study. Environmental Research. 97(3): 312-321.

92. Woodruff, T.J., Darrow, L.A., Parker, J.D. (2008). Air pollution and postneonatal infant mortality in the United States, 1999-2002. Environmental Health Perspectives. 116(1):110-115.

93. Young, M.T., Sandler, D.P., DeRoo, L.A., Vedal, S., Kaufman, J.D., London, S.J. (2014). Ambient air pollution exposure and incident adult asthma in a nationwide cohort of U.S. women. American Journal of Respiratory and Critical Care Medicine. 190(8):914-921.

94. Zanobetti, A. and Schwartz, J. (2008a). Mortality Displacement in the Association of Ozone with Mortality: An Analysis of 48 U.S. Cities. American Journal of Respiratory and Critical Care Medicine. 177(2):184-189.

95. Zanobetti, A. and Schwartz, J. (2008b). Is there adaptation in the ozone mortality relationship: A multi-city case-crossover analysis. Environmental Health. 7(22):

96.   Zanobetti, A., Schwartz, J. (2011). Ozone and survival in four cohorts with potentially predisposing diseases. American Journal of Respiratory and Critical Care Medicine. 184(7): 836-841.

97.   Zhu, Z., Liu, Y., Chen, Y., Yao, C., Che, Z., Cao, J. (2015). Erratum to: Maternal exposure to fin particulate matter ($PM_{2.5}$) and pregnancy outcomes: a meta-analysis. Environmental Science and Pollution Research. 22:3397-3399.